Editorial

Intercellular transmission of endoplasmic reticulum stress through gap junction targeted by microRNAs as a key step of diabetic kidney diseases?

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Diabetic kidney disease (DKD) is a type of renal diseases caused by Diabetes Mellitus (1-4). Renal fibrosis and hypertrophy by accumulated extracellular matrix (ECM) proteins in glomerular and tubular compartments, as well as podocyte dysfunction and related albuminuria are major features of DKD. Metabolic changes such as mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress (ERS) and loss of autophagy in renal cells are also associated with progressive DKD (4-7). Non-coding RNAs including microRNAs (miRNAs) and long-non-coding RNAs (lncRNAs) are now very attractive regulators of gene expression because of their no protein-coding potential and because miRNAs regulate cellular functions and pathophysiological conditions related to human disease including DKD by down-regulating their specific targets (4,8-11).

A recent report by Li *et al.* showed that miR-30 family members (miR-30s) directly target connexin 43 (Cx43) (12), a Gap junction protein which mediates cell-cell transmission of ions, signaling molecules, metabolites and nucleic acids (13,14). The decrease of miR-30s induces Cx43 which enhances ERS-related caspase12 and apoptosis in cultured podocytes treated with high glucose conditions (HG) and in kidneys from diabetic rats (*Figure 1A*). Silencing of Cx43 by siRNAs inhibited ERS and apoptosis induced by HG in podocytes. Cx43 has been suggested as molecular target of kidney diseases and activates ERS (15-18). The authors also showed that adeno-associated virus (AAV)-mediated induction of miR-30s ameliorated kidney injury in diabetic rats, suggesting that miR-30s/Cx43/ERS axis may be a new potential target for DKD.

On the other hand, another recent paper reported that ERS can be transmitted from cell to cell through Cx43 and spreading ERS may cause liver diseases and problems such as insulin resistance (19). Therefore, global spread of ERS through Gap junction (Cx43) may also contribute to the injury and death of podocytes (and even other renal glomerular cells) (*Figure 1B*). Thus, the event is not simply happening in single cells but local ERS in single cells may be spread into multiple adjacent cells and cause global increase of ERS in kidney glomeruli (not only in podocytes) and eventually lead to kidney injury (*Figure 2*).

Although the molecular mechanisms of miR-30s reduction by HG in podocytes are not clear (12), Gap junction may also explain how miR-30s levels were reduced, because transmission of miR-30s from healthy cells to stressed cells may dilute the intracellular concentration of miR-30s (*Figure 1B*). While miRNAs usually control target gene expression (8), endogenous RNAs also control miRNAs by target RNA-directed miRNA degradation (TDMD) (20-22). Recent reports have demonstrated the strong evidence of TDMD (22-25) and miR-30s have been reported as one of such miRNAs subjected to TDMD (25). Although it is depending on the members, at least miR-30b/c

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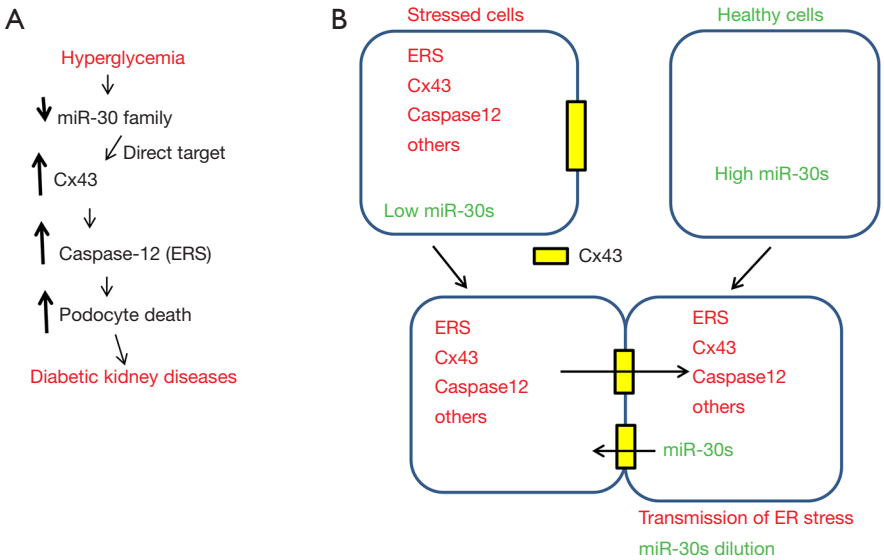

Figure 1 Mechanisms of ERS activation and cell-cell transmission via Cx43. (A) A model for the pathogenesis of DKD through miR-30/Cx43/ERS. (B) Possible intercellular transmission of ERS (also Caspase12, Cx43, miR-30s and others) between stressed cells and healthy cells through Cx43. Please read the main text for more details. ERS, endoplasmic reticulum stress; Cx43, connexin 43; DKD, diabetic kidney disease; miR-30s, miR-30 family members.

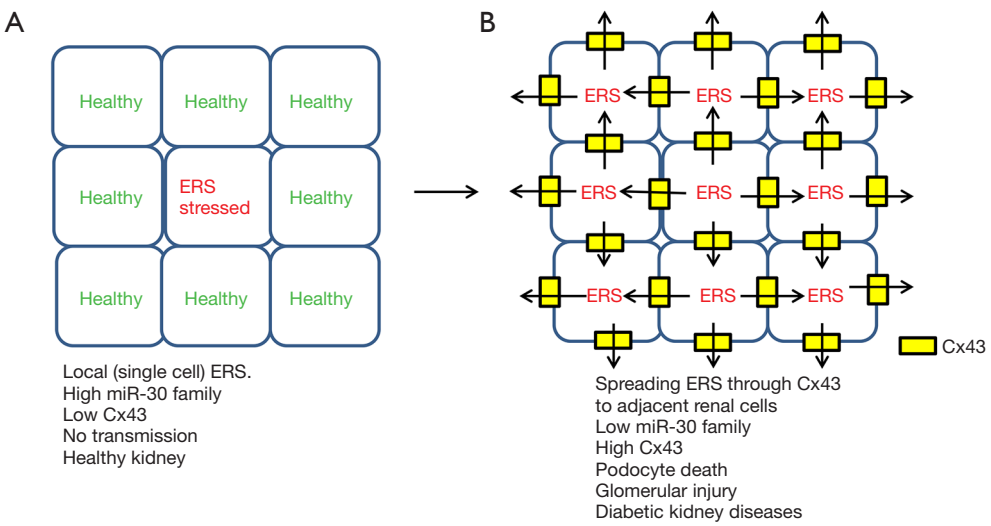

Figure 2 ERS spread from stressed single cells to multiple adjacent cells through Cx43. (A) Healthy or non-disease conditions. Even if one stressed cell exists, other cells are not affected (healthy). (B) Spreading ERS from single cell (center) to adjacent multiple cells through Cx43 increased in diabetic conditions. Please read the main text for more details. ERS, endoplasmic reticulum stress; Cx43, connexin 43.

are regulated by target RNA (Serpin1) (25). Therefore, miR-30s may also be regulated by the other target RNAs such as Cx43 mRNA which is potentially transmitted from stressed cells to destroy miR-30s in healthy cells.

Identifying new therapeutic targets for DKD is crucial now. As shown in the recent study (12), intercellular transmission of ERS through Gap Junction targeted by miR-30s may be a new key step of DKD. miRNA studies provided us numerous unexpected discoveries. Controlling such miRNAs using the knowledge obtained from the study

on RNA biogenesis might provide new effective ways to treat or prevent the disease progression in the future.

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